INTRODUCTION

General Principles of Monitoring of Disease-Modifying Antirheumatic Drugs

Prolonged therapy with disease-modifying antirheumatic drugs (DMARDs) requires long-term monitoring for toxicity and safety profile. Whatever DMARD is considered appropriate for a patient, it is paramount that the patient is carefully monitored so that there is no delay in the detection of any untoward effect of the drug. Monitoring will also contribute to assessing activity of the underlying disease.

Disease-modifying antirheumatic drugs are slow acting drugs which may take weeks to months to produce any clinical response. Patients need to be informed about the delayed action of these drugs and the need to persevere with the treatment (in the absence of side effect).

In addition to absolute values for any hematological or biochemical indices, a rapid unusual fall or rise or a consistent downward or upward trend in any value should prompt caution and extra vigilance. Details of monitoring schedules should be recorded in the patients’ case notes and should be provided with access to the results of their monitoring. Wherever possible, as part of a self-management program, patients should be encouraged to take responsibility for monitoring their own therapy. The recommendations for optimal timing of monitoring are based on clinical experience, as there is little evidence to inform the optimal timing of monitoring schedules.

Baseline Studies

Recommended screening prior to starting, resuming, or significantly increasing therapy with nonbiologic or biologic DMARDs includes:

- All patients—complete blood count (CBC) and serum creatinine and aminotransferases
- Prior to methotrexate (MTX), leflunomide (LEF) or biologic DMARDs—screening for hepatitis B and C should be performed in patients at increased risk
- Hydroxychloroquine—a complete baseline ophthalmologic examination within the first year of treatment, including examination of the retina through a dilated pupil and testing of central visual field sensitivity
- Testing for latent tuberculosis (TB)—the 2008 American College of Rheumatology (ACR) guidelines recommended screening for latent TB with skin testing prior to all biologic DMARDs based upon evidence that tumor necrosis factor (TNF) inhibitors increase the risk of mycobacterial infection. A possible exception is rituximab, since there is no clear evidence of an increased risk of TB with this agent. A chest radiograph is recommended in patients with a history of other risk factors for latent TB, and skin testing should be repeated in patients with new TB exposures.

MONITORING OF NONBIOLOGIC DMARDs

Sulfasalazine

Placebo-controlled trials have demonstrated that sulfasalazine is an efficacious DMARD in the treatment of rheumatoid arthritis (RA). It has been shown to slow the progression of erosive changes on X-ray also.

Minor side effects include nausea, which is often transient during the first few days of treatment. Skin rash, typically maculopapular and pruritic, occurs in 4–5% of patients. Stevens-Johnson syndrome has been reported. Reversible oligospermia may result in reduced fertility. More serious side effects, including potentially fatal neutropenia or aplastic anemia, are rare. The incidence of sulfasalazine-induced neutropenia has been estimated to be as high as 2% in RA patients but most cases are reversible on withdrawal of the drug.

Methotrexate

Several randomized placebo-controlled trials have shown that MTX has a significant beneficial effect on disease activity in RA. MTX has also been shown to slow the rate of progression of erosions and joint space narrowing in radiographic studies.

Many of the side effects are due to the inhibition of folate metabolism (e.g., nausea, stomatitis, bone marrow suppression). As the beneficial effects of MTX in RA are largely unrelated to folate inhibition, the administration of a single weekly dose of folic acid, 5–10 mg, can result in a significant reduction in toxicity without loss of efficacy.

Methotrexate outperformed other DMARDs in a meta-analysis of studies comparing efficacy with toxicity, and more patients remained on MTX after 5 years than on other DMARDs. However, enthusiasm for the use of MTX is limited by two potentially serious adverse reactions which may not resolve with cessation of treatment:

1. Liver disease: Methotrexate-induced liver disease is characterized by fibrotic changes which may progress to cirrhosis. Initial studies...
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overestimated the incidence and seriousness of MTX induced liver disease. The incidence of real toxicity is probably in the
order of 1 in 1,000 RA patients over a 5-year treatment period.6 While
routine liver biopsy is not recommended, patients who have
persistent elevation of aspartate aminotransferase (AST) may require
a liver biopsy to ensure that continuation of treatment is not
harmful.6

2. Interstitial pneumonia: This is an uncommon but potentially
fatal complication of MTX treatment. The risk factors for MTX lung
are not well understood, but may include pre-existing lung disease or
an abnormal chest radiograph. Patients taking MTX who present
with dry cough, shortness of breath on exertion, malaise, fever
and diffuse crackles on auscultation should discontinue taking
MTX until evaluated further. The chest X-ray may be normal. The
differential diagnosis includes Pneumocystis carinii pneumonia,
and bronchoscopy may be required to exclude this.

Monitoring Recommendations

Baseline CBC, LFTs, serum creatinine and chest X-ray. X-ray
chest need not to be repeated unless clinician suspects some lung
involvement. CBC, LFTs and serum creatinine every 4-8 weeks.
The MTX need not be discontinued unless transaminases are raised
more than two times the normal value.

Note: Methotrexate is given as a weekly dose in RA. There have
been overseas reports of patients who developed serious side effects
following the inadvertent administration of MTX as a daily dose.

Antimalarials

Chloroquine and hydroxychloroquine have both been used for
the treatment of RA, although controlled studies of antimalarials
in RA have almost all involved hydroxychloroquine, and toxicity
is thought to be greater with chloroquine. Several randomized
controlled trials have shown that hydroxychloroquine is superior
to placebo with regard to disease activity in the treatment of RA.
Hydroxychloroquine and sulfasalazine were found to have similar
effects on disease activity, although sulfasalazine was significantly
superior to hydroxychloroquine in preventing joint damage
measured radiographically.

Minor side effects include nausea and rash. Bone marrow
suppression is rare, but potentially fatal agranulocytosis or aplastic
anemia can occur. Monitoring the blood count is not generally
considered necessary. Much attention has been given to the corneal
and retinal damage that may occur following treatment with
antimalarials. A recent study has shown that RA patients taking a
daily dose less than 6.5 mg/kg of hydroxychloroquine were not at
increased risk of ocular complications.

Monitoring Recommendations

Baseline serum creatinine. Routine review by an ophthalmologist
every 6-12 months in those taking greater than 6.5 mg/kg/day
hydroxychloroquine, and/or those with renal impairment or in the
elderly or duration of treatment greater than 10 years.7,8

Leflunomide

A range of potential adverse effects may occur. LEF has been reported
in some patients to potentiate the action of warfarin as a result of its
mutual competition at the level of cytochrome metabolism.

Hypertension: A small percentage of patients with RA develop
hypertension when taking LEF. Concurrent therapy with
nonsteroidal anti-inflammatory drugs (NSAIDs) is a risk factor.
The proposed mechanism is the displacement of NSAIDs from
albumin by teriflunomide, thereby increasing NSAID activity.

Blood pressure monitoring is recommended during the first
months of treatment or if NSAID therapy is begun at a later date.

Gastrointestinal: Diarrhea and nausea occur in 10-15% of patients
taking LEF. These side effects are seldom severe enough to lead to
drug discontinuation. Diarrhea may be more severe with a loading
dose, which, as noted above, is not recommended.

Liver: Threefold elevation of serum aminotransferases have been
noted in up to 13% of patients treated with LEF. During the past
decade, the general opinion has been that careful monitoring of LEF
allowed it to be used with a safety comparable to MTX. The changes
in liver function are generally reversible with dose reduction or
discontinuation of the drug. However, 49 cases of severe liver injury,
including 14 cases of fatal liver failure, were reported to the US Food
and Drug Administration (FDA) between August 2002 and May
2009. Most patients who experience transaminase elevation have
one or more comorbidities that might contribute to hepatotoxicity,
including concomitant NSAID or MTX therapy, previous or
concurrent alcohol abuse, or viral or autoimmune hepatitis. The FDA
has issued the below warnings based upon these observations:

- Patients with pre-existing liver disease should not receive LEF.
- Patients with elevated liver enzymes [alanine aminotransferase
  (ALT) greater than two times the upper limit of normal] should
  not receive LEF.
- Caution should be used in patients who are taking other drugs
  that can cause liver injury.
- Liver enzymes should be monitored at least monthly for 3 months
  after starting LEF and at least quarterly thereafter.
- If the ALT rises to greater than two times the upper limit of normal
  while the patient is on LEF, leflunomide should be stopped,
  cholestyramine washout begun to speed the removal of LEF from
  the body and follow-up LFTs conducted at least weekly until the
  ALT value is within normal range.

These FDA recommendations for monitoring frequency are
consistent with those of the 2008 ACR recommendations on use of
LEF in RA.1,9

American College of Rheumatology guidelines state that patients
receiving MTX and LEF concurrently, be monitored monthly for 1
year, including serum albumin and aspartate and ALT levels, after
which the monitoring interval may be increased to every 2 months.

Leukopenia: Estimates of incidence in patients taking LEF alone
ranged from 1 in 3,698 to 1 in 4,582 patients exposed; for patients also
taking MTX the estimates ranged from 1 in 575 to 1 in 822.

Lung: Leflunomide treatment has been associated with an increased
risk of interstitial lung disease. However, it is not clear whether this is
a true effect or the result of “channeling bias”, in which patients with
pre-existing interstitial lung disease are more likely to be treated with
LEF than with MTX, which is known to cause this complication.

Peripheral nerves: Peripheral neuropathy occurs in some patients
treated with LEF. A review of 80 cases reported to the US FDA
noted that symptoms of peripheral nerve dysfunction, typically
characterized by axonal polyneuropathy, began a mean of 6 months
after beginning the drug. Discontinuation of LEF within 30 days of
the onset of symptoms was associated with a better outcome than
stopping at a later time. In another study, 5 of 50 RA patients treated
with LEF developed symptoms of peripheral neuropathy, but all
improved after stopping the drug.

Skin: Rash and alopecia occur in 10-15% of patients taking LEF.
These side effects are typically mild and seldom lead to drug
discontinuation.
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**Hematology:** Hematologic toxicity primarily results from an interaction between LEF and other drugs. LEF may enhance the bone marrow toxicity of MTX, possibly leading to pancytopenia, agranulocytosis or thrombocytopenia.

Leflunomide can potentiate the anticoagulant effect of warfarin. As a result, the International Normalized Ratio (INR) should be more carefully monitored after initiation of LEF in patients taking warfarin.

**Neuropathy:** Peripheral neuropathy has been reported in patients receiving LEF with partial improvement after drug removal with cholestyramine. Similarly, a case of aseptic meningitis that improved with drug removal has also been reported.

**Contraindications**

Leflunomide is contraindicated in pregnant and nursing women and in patients with pre-existing liver disease. If LEF is taken during pregnancy or if the patient becomes pregnant while taking LEF, elimination of the drug can be accelerated through the administration of cholestyramine (8 g orally three times daily for 11 days).

**Gold Compounds**

Although auranofin has been shown to be superior to placebo in the treatment of RA, it is less efficacious than injectable gold. Auranofin has a low incidence of serious toxicity, but the overall frequency of side effects (e.g. rash, diarrhea) is higher with auranofin than with any other DMARD. Its usefulness is, therefore, limited by low efficacy and poor tolerability.

Sodium aurothiomalate (Myocrisin) is an injectable gold salt which has been shown to have a similar efficacy to sulfasalazine. D-penicillamine and MTX, but with consi-derably greater toxicity than these drugs. There is conflicting data on the question of whether injectable gold prevents progression of radiographic erosions. Side effects may include rash, stomatitis, thrombocytopenia, proteinuria and nephrotic syndrome. Interstitial pneumonitis (gold lung) is a rare but potentially fatal complication of gold treatment.

**Monitoring Recommendations**

Baseline CBC, creatinine and urine dipstick for protein. CBC and urine dipstick for protein every 2 weeks until dosage stable, then every 1–3 months.10

**Azathioprine**

Its efficacy has been found to be comparable to hydroxy-chloroquine, D-penicillamine and cyclosporine. In Felson’s meta-analysis, azathioprine had similar toxicity to sulfasalazine and MTX, but was less efficacious. Its efficacy was similar to that of antimalarials, but it had greater toxicity.11

Transient side effects may include nausea, stomatitis and bone marrow suppression. Hepatitis and pancreatitis are uncommon. There has been concern about a potential increased risk of lymphoma. While transplant recipients are at increased risk of lymphoma, there is conflicting evidence for an increased risk of lymphoproliferative malignancy in RA patients.

**Monitoring Recommendations**

Baseline CBC, serum creatinine, LFTs. CBC every 1-3 months.

**D-Penicillamine**

In doses greater than 500 mg/day, D-penicillamine has been shown to beneficial in the treatment of RA. It has been shown to have efficacy similar to MTX, injectable gold, azathioprine and hydroxychloroquine. There is no evidence that D-penicillamine slow the progression of radiographic damage. Adverse effects may include rash, alopecia, altered taste, stomatitis and gastrointestinal upset. Leukopenia, thrombocytopenia and aplastic anemia can occur, as can hematuria and the nephrotic syndrome which require monitoring. Rarely, autoimmune syndromes, including SLE, polymyositis, Goodpasture’s syndrome and myasthenia gravis may develop.

**Monitoring Recommendations**

Baseline CBC, creatinine and urine dipstick for protein. CBC and urine dipstick for protein every 2 weeks until dosage stable, then every 1–3 months.12

**Cyclosporine A**

In placebo-controlled trials, cyclosporine has been shown to improve clinical manifestations of RA, and to reduce the progression of radiographic erosions.

The most important adverse effect is nephrotoxicity which must be monitored with blood pressure recordings and serum creatinine measurements. This may be acute, mediated by renal vasoconstriction, or chronic, resulting in permanent damage to the kidneys. The risk of gingival hyperplasia may be lessened with meticulous oral hygiene. Other side effects include hirsutism, tremor, paresthesia and headache.

**Monitoring Recommendations**

Baseline CBC, creatinine (on two different occasions), uric acid, LFTs and blood pressure (on two different occasions). Serum creatinine every 2 weeks until dosage stable, then monthly. Periodic CBC, electrolytes and LFTs.12

**RELATIVE EFFICACY AND TOXICITY OF DMARD**

Life table analysis studies which compare the dropout rates for the use of DMARDs reflect the efficacy of a drug as perceived by patient and physician, as well as the ability of the patient to tolerate the side effects of that drug. In these studies, the number of patients who continued to benefit from and tolerate MTX after 5 years was approximately twofold greater than for other DMARDs. In a meta-analysis based on existing clinical trials which compared efficacy with toxicity, MTX and sulfasalazine were found to have relatively high efficacy and low toxicity. Antimalarials had moderate efficacy and low toxicity, but intramuscular gold had moderate efficacy but relatively high toxicity. An index of the relative toxicity of DMARDs has been derived from a study of 2,747 RA patients. Hydroxychloroquine was the least toxic with an index of 1.38. MTX had an index of 3.82, and this was lower than several of the NSAIDs studied (e.g. indomethacin 3.99). The findings of these studies are in line with current practice which favors the use of MTX, sulfasalazine and hydroxychloroquine over other agents such as D-penicillamine, azathioprine and gold salts.10

**TREATMENT STRATEGIES AND COMBINATION THERAPY**

Although reports of the treatment of RA with a combination of DMARDs date back nearly 40 years, it is only recently that the practice has become widespread. The recognition of the morbidity and mortality associated with RA, and the ability to predict prognosis has led to a more aggressive approach to treatment in high-risk individuals.

The step-down approach has been proposed for the treatment of patients with recent onset RA who have clinical features predictive of an adverse prognosis. This may involve a combination of two or more DMARDs, corticosteroids and NSAIDs given at the onset and then withdrawn in a stepwise fashion once remission is achieved. Others favor the sequential addition of DMARDs to minimize
toxicity. Numerous DMARD combinations have been evaluated but those involving any two or all three of MTX, sulfasalazine and hydroxychloroquine have been particularly effective. Surprisingly, the combination of MTX and sulfasalazine does not appear to be more toxic than either drug used as monotherapy.

**MONITORING OF BIOLOGICS**

**Pretreatment Screening and Monitoring**

For first generation (adalimumab, etanercept and infliximab) and second generation anti-TNF-α therapies (certolizumab pegol and golimumab), blood monitoring should be undertaken before starting treatment. The minimum monitoring required should fulfill the criteria for monitoring of MTX or other DMARDs which are coprescribed with biologic therapies. Autoantibodies are not routinely taken before commencing treatment, but may be necessary if the patient develops symptoms suggestive of lupus.

Before starting treatment, take the following:
- Chest X-ray, full blood count (FBC), urea and electrolytes (U and E) LFTs, test for hepatitis B and C.

**Risk of Infection: General Areas for Caution**

All patients being considered for a biologic therapy must be screened to exclude the risk of any infection, including TB. If serious infections are evident before treatment, they should be reviewed by the prescribing physician and fully resolved before considering treatment with a biologic. If a serious infection develops, treatment should be stopped and only restarted once the infection has completely resolved. Ensure the patient is aware of their own responsibility for reporting any clinical signs and symptoms that might indicate an infection.

**Contraindications**

The contraindications to TNF inhibitor use are the same as those for use in other diseases, such as RA.1,2,13

Briefly summarized, the contraindications to the use of anti-TNF therapies include the following:
- Active infection
- Latent (untreated) TB
- Demyelinating disease (e.g. multiple sclerosis, optic neuritis)
- Heart failure
- Pregnancy and breast-feeding

**Vaccines**

- All patients receiving TNF-α inhibitors should receive the pneumococcal vaccine, and inactivated influenza vaccine annually.
- Those with specific risk factors should also be vaccinated against hepatitis B.
- Vaccines containing live organisms should not be administered during treatment with TNF-α inhibitors.
- Clinicians should ensure that patients are up to date on age-appropriate vaccinations before starting a course of TNF-α inhibition.
- Initiation of TNF-α inhibitor therapy should be delayed after administration of a live organism vaccine.

**Risk of Tubercular Infection**

*Tumor necrosis factor-α* inhibitors increase the risk of reactivation of latent TB infection. This risk is greater for the anti-TNF antibodies infliximab and adalimumab than for etanercept. The United States Centers for Disease Control and Prevention recommends treatment of latent TB infection (LTBI) prior to starting a TNF-α inhibitor. In addition, when active TB infection is diagnosed in a patient receiving a TNF-α inhibitor, this agent should be discontinued and treatment for active TB should be initiated.

**Latent TB infection:** The CDC recommends treatment of LTBI for all patients planning to take a TNF-α inhibitor who have a tuberculosis skin test (TST) result of greater than or equal to 5 mm induration or a positive interferon-gamma release assay (IGRA).

TNF-α inhibitor candidates with a negative TST (< 5 mm) or IGRA should also be treated for LTBI if there is evidence of remote TB disease on chest radiography (e.g. regional fibrosis with or without hilar lymphadenopathy) or if there is epidemiologic evidence of prior TB exposure (e.g. having had close contact to a TB case, or having resided in a country of high TB incidence).

**Summary of Monitoring During Treatment with Biologics**1,2,13

- **History and examination:**
  - Symptoms and signs of infection
  - Symptoms and signs of congestive heart failure
  - Symptoms and signs of demyelinating disease
- **Chest X-ray:**
  - Repeat chest X-ray after 6 months of treatment to screen for TB
- **Laboratory tests** (Etanercept and adalimumab—monthly; infliximab—before each infusion):
  - Full blood count
  - Alanine aminotransferase or AST; serum creatinine

**Other Biologics**

- **Tocilizumab: monitoring parameters,**13
  - Signs and symptoms of infection (prior to and during therapy);
  - Tocilizumab monitoring prior to therapy initiation; CBC with differential [prior to and every 2–4 weeks (systemic juvenile idiopathic arthritis) or 4–8 weeks (RA) during therapy]; ALT/AST [prior to and every 2–4 weeks (systemic onset juvenile idiopathic arthritis) or 4–8 weeks (RA) during therapy]; additional LFTs as clinically indicated; lipid panel (prior to, at 4–8 weeks following initiation, and every 6 months during therapy); signs and symptoms of central nervous system (CNS) demyelinating disorders.
- **Rituximab: monitor the following:**
  - Infusion reactions (30–35% with the first infusion)
  - Hypogammaglobulinemia and infection—total immunoglobulin (Ig) levels following one course of therapy with rituximab may be associated with a higher rate of serious infections.
  - Rituximab has been associated in case reports with severe *Pneumocystis carinii* (P. jirovecii) infection,17 cytomegalovirus colitis,18 progressive multifocal leukoencephalopathy (PML),20
- **Abatacept:**
  - The efficacy and safety of abatacept in RA has been analyzed in a 2009 meta-analysis, which included seven randomized trials with 2,908 patients and which compared abatacept alone or in combination with nonbiologic or biologic DMARDs with placebo alone or in combination with nonbiologic or biologic DMARDs.21,22
There has been a significantly increased number of serious infections at 12 months in the abatacept-treated patients, a finding consistent with trends observed in another meta-analysis. Treatment of RA patients with abatacept has not been associated with an increased frequency of malignancy in the abatacept clinical trials participants.

**SUMMARY**

- Disease-modifying antirheumatic drugs are fundamental to arresting the disease process in RA and other inflammatory arthritides.
- Many are also used for other licensed and unlicensed indications, such as chronic inflammatory skin or bowel disease.
- While early initiation of therapy is essential, sustained use is vital if disease suppression is to be maintained, and so these drugs may be used for an unlimited period of time.
- Prolonged therapy requires long-term monitoring for toxicity and safety profile.
- Whatever DMARD is considered appropriate for a patient, it is paramount that the patient is carefully monitored so that there is no delay in the detection of any untoward effect of the drug.
- Monitoring will also contribute to assessing activity of the underlying disease.

**CONCLUSION**

- The use of DMARDs in rheumatology thus requires the standard guidelines for drug toxicity monitoring, as adverse effects can be significant in some patients.
- The adverse effects of DMARDs as reported in research trials have limitations, as the patient characteristics are likely to be different from those in daily clinical practice.
- It is necessary, to have some form of guideline which is multidisciplinary with patient participation, using evidence base, peer reviewed, well researched and supported by some study/audit of national practice. With greater accumulation of evidence, the need for a comprehensive guideline is, therefore, not only timely but also of paramount importance as the approach to therapy of many rheumatological diseases has changed in the recent years.

**REFERENCES**